

A projection argument for differential inclusions, with applications to persistence of mass-action kinetics

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3 August 2012

Abstract

Motivated by questions in mass-action kinetics, we introduce the notion of *vertexical family* of differential inclusions. Defined on open hypercubes, these families are characterized by particular good behavior under projection maps. The motivating examples are certain families of reaction networks—including reversible, weakly reversible, endotactic, and *strongly endotactic* reaction networks—that give rise to vertexical families of mass-action differential inclusions. We prove that vertexical families are amenable to structural induction. Consequently, a trajectory of a vertexical family approaches the boundary if and only if either the trajectory approaches a vertex of the hypercube, or a trajectory in a lower-dimensional member of the family approaches the boundary. With this technology, we make progress on the global attractor conjecture, a central open problem concerning mass-action kinetics systems. Additionally, we phrase mass-action kinetics as a functor on reaction networks with variable rates.

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1 Introduction

The global attractor conjecture has been a central open problem in reaction network theory since its formulation by Horn in 1974 [14]. It asserts that any complex-balanced mass-action kinetics system of ordinary differential equations with positive initial conditions possesses a globally attracting stationary point in each stoichiometric compatibility class (see Conjecture 6.1 for a more precise statement). It is well-known that this conjecture is implied by Feinberg’s persistence conjecture [11], a version of which asserts the following: for weakly reversible networks taken with mass-action kinetics, no species asymptotically becomes extinct or unbounded. An a priori special case of the persistence conjecture asserts that at least one species survives asymptotically. In this paper, we show that this a priori special case in fact implies the entire persistence conjecture (Corollary 6.2). As a consequence, if the persistence conjecture is false, then in every minimal counterexample each species becomes either extinct or unbounded. It follows that the persistence conjecture in dimension n implies the global attractor conjecture in dimension $n + 1$.

Pantea [18], building on earlier work by Craciun, Nazarov, and Pantea [7], used the persistence conjecture in two dimensions to prove the global attractor conjecture in three dimensions. Pantea’s work relied in part on projecting trajectories to lower-dimensional faces. Here, we generalize this projection argument in two ways. First, our main result, Theorem 3.13, applies in arbitrary dimensions. Second, our results hold not only for mass-action kinetics networks, but for certain families of differential inclusions that we call *vertexical* (Definition 3.12). The notion of vertexical family makes precise the essential structure required of a family of dynamical systems on hypercubes of varying dimensions to permit a structural induction argument of this sort. Theorem 3.13 shows that a trajectory in a vertexical family approaches the boundary if and only if either it approaches a vertex of the hypercube, or a lower-dimensional trajectory in the family approaches the boundary.

Vertexical families of differential inclusions arise naturally in reaction network theory by way of mass-action kinetics on networks that are reversible, weakly reversible, endotactic, strongly endotactic (Definition 4.9.4), and so on. We prove that these networks, and more generally, *projective classes* of networks (Definition 5.1), give rise to vertexical families of mass-action differential inclusions (Theorem 5.19 and Corollary 5.20). In the course of proving this result, we are led to view mass-action kinetics as a functor (Theorem 5.17). Doing so clarifies the concept of vertexical family and suggests that other questions concerning mass-action kinetics systems may be amenable to structural induction. Finally, Section 6 discusses the implications of our results for persistence of mass-action kinetics systems.

Acknowledgements. MG was supported by a Ramanujan fellowship from the Department of Science and Technology, India, and, during a semester-long stay at Duke University, by the Duke MathBio RTG grant NSF DMS-0943760. EM had support from NSF grant DMS-1001437. AS was supported by an NSF postdoctoral fellowship DMS-1004380. The authors thank David F. Anderson, Gheorghe Craciun, and Casian Pantea for helpful dis-

cussions, and Duke University where many of the conversations occurred.

2 Dynamical properties of differential inclusions

In this section, we recall certain dynamical properties of differential inclusions defined on manifolds. For background on manifolds, see [17]. All manifolds considered here have finite dimension.

Definition 2.1. Let M be a smooth manifold. Let $\pi_M : TM \rightarrow M$ be the tangent bundle of M . A *differential inclusion* on M is a subset $X \subseteq TM$.

Example 2.2. The simplest differential inclusions on M are vector fields on M . The subset $X \subseteq TM$ for a given vector field is the image of the corresponding section $M \hookrightarrow TM$.

Definition 2.3 (Trajectory). Fix a differential inclusion X on a smooth manifold M . Let $I \subseteq \mathbb{R}_{\geq 0}$ be a nonempty interval (in particular, connected) containing its left endpoint. A differentiable curve $f : I \rightarrow M$ is a *trajectory* of X if the tangent vectors to the curve lie in X . An unbounded interval is a *ray*. A trajectory defined on a ray *eventually* has a property P if there exists $T > 0$ such that property P holds for the function for all $t \geq T$.

A smooth manifold with corners \overline{M} is a space locally modeled on the closed nonnegative orthant [17, p. 363]. The relative interior $\overline{M} \setminus \partial\overline{M}$ of a manifold with corners is a smooth manifold [17, p. 386, Ex. 14–19].

Definition 2.4. Fix a smooth manifold with corners \overline{M} with relative interior $M = \overline{M} \setminus \partial\overline{M}$, and let $V \subseteq \partial\overline{M}$ be a subset of the boundary. A differential inclusion $X \subseteq TM$ is

1. *persistent relative to V* if the closure in \overline{M} of every trajectory of X is disjoint from \overline{V} .
2. *repelled by V* if for every open set $O_1 \subseteq \overline{M}$ with $\overline{V} \subseteq O_1$, there exists a smaller open set $O_2 \subseteq O_1$ with $\overline{V} \subseteq O_2$ such that for every trajectory $f : I \rightarrow M$ of X , if $f(\inf I) \notin O_1$ then $f(I) \cap O_2 = \emptyset$; in other words, if the trajectory begins outside of O_1 , then the trajectory never enters O_2 .
3. *permanent relative to V* if it is persistent and there is a compact subset $\Omega \subseteq \overline{M} \setminus \overline{V}$ such that for every ray I , every trajectory of X defined on I is eventually contained in Ω .

More generally, a set \mathcal{X} of differential inclusions on M is *persistent relative to V* , *repelled by V* , or *permanent relative to V* if every member $X \in \mathcal{X}$ has the corresponding property.

Remark 2.5. Any differential inclusion repelled by V is also persistent relative to V . The converse is false in general because different trajectories starting outside O_1 could get arbitrarily close to V . However, if \overline{M} is compact, then it can be shown that this does not happen without violating persistence. Therefore, repelled and persistent are the same property for compact manifolds with corners.

Remark 2.6. A differential inclusion that is permanent relative to V need not be repelled by V when \overline{M} is not compact. (When M is compact, see Remark 2.5.) The reason appeared already in Remark 2.5: different trajectories starting outside O_1 could get arbitrarily close to V . The crux is that the eventuality condition defining permanence does not apply to trajectories defined on finite intervals. On the other hand, if every trajectory defined on a finite interval can be extended infinitely—that is, can be extended to a trajectory defined on a ray—then in fact V does repel any differential inclusion that is permanent relative to V .

Conversely, a differential inclusion repelled by V need not be permanent relative to V , even if \overline{M} is compact, because O_2 might necessarily be smaller when O_1 is smaller. That is, trajectories that start closer to V could eventually remain closer to V , as in Example 2.7.

Example 2.7. Fix a differential inclusion X on a planar disk \overline{M} whose trajectories form concentric circles about its center. X is repelled by the boundary circle $V = \partial\overline{M}$. Indeed, if $O_1 \subseteq \overline{M}$ is an open set containing V , then the compact set $\overline{M} \setminus O_1$ achieves a maximum radius r from the center, so we can take O_2 to be the set of all points in \overline{M} of radius $> r$.

Lemma 2.8. *If the differential inclusion X in Definition 2.4 is persistent, then for every trajectory $f : I \rightarrow M$ of X , there exist disjoint open sets O_f and O_V in \overline{M} containing the closures in \overline{M} of $f(I)$ and V respectively.*

Proof. A manifold with corners is metrizable, and hence it is a normal Hausdorff space. \square

Remark 2.9. Even with Lemma 2.8, our definition of persistence is weaker than the standard definition [12] that requires each coordinate of a trajectory to remain bounded away from 0 for all time. However, we follow other works in the chemical reaction network literature [3, 5] in using Definition 2.4.1. Additionally, Definition 2.4.1 agrees with the sense in which Feinberg first stated the persistence conjecture (see Section 6).

Mathematically, the definition we adopt has the advantage of being purely topological, so it behaves well under homeomorphism. Our definition also separates the usual concept of persistence into the two questions of whether trajectories are bounded and whether ω -limit points exist on the boundary. Both properties are conjectured to hold for weakly reversible and, more generally, endotactic (see Definition 4.9) reaction networks. When trajectories are bounded, our definition of persistence is equivalent to the standard one.

Remark 2.10. Suppose a manifold M has a metric d , and V is a compact subset of M . A differential inclusion X is repelled by V if for every $d_1 \in \mathbb{R}_{>0}$, there exists $d_2 \in \mathbb{R}_{>0}$ such that $d(f(I), V) \geq d_2$ for every trajectory $f : I \rightarrow M$ of X satisfying $d(f(\inf I), V) \geq d_1$.

Definition 2.11. Differential inclusions that are persistent relative to the boundary $\partial\overline{M}$ are simply called *persistent*, and similarly for *permanent* and *repelled*. A collection of differential inclusions, possibly on a family of different manifolds with corners, is *persistent*, *permanent*, or *repelled* if each differential inclusion in the collection has the respective property.

Remark 2.12. Our use of the term “repelled” is related to other usages. Anderson and Shiu defined a boundary face to have a “repelling neighborhood” if the description in Remark 2.10 holds: if there is a neighborhood of the face such that whenever a trajectory is in that neighborhood, it can get no closer to the face while remaining in that neighborhood [2]. A different definition is that of a “repelling face” which Banaji and Mierczynski used to describe a boundary face for which any trajectory that begins in that face immediately exits the face into the interior of the relevant invariant set [6].

Remark 2.13. Suppose a differential inclusion X is a subset of a persistent differential inclusion Y . Then X must be persistent, since its trajectories are all automatically trajectories of Y . More generally, consider properties P of differential inclusions X of the form “ $P(f)$ holds for all trajectories f of X .” If property P is true for a differential inclusion Y , and a differential inclusion Z factors through Y , then property P is true for Z as well.

3 Vertexical families of differential inclusions

A mass-action kinetics system is naturally defined on the positive orthant $\mathbb{R}_{>0}^S$ corresponding to the space of concentrations of species. In this section we work instead with open hypercubes $(0, 1)^S$, and not directly with positive orthants themselves.

To justify this choice, first we argue that little is lost by working with hypercubes. Open hypercubes $(0, 1)^S$ are diffeomorphic to positive orthants $\mathbb{R}_{>0}^S$, so differential inclusions can be transferred from one space to the other by fixing a diffeomorphism and using its Jacobian (see Section 5.2). Additionally, properties such as persistence are defined topologically on the tangent bundle—and therefore invariant under diffeomorphism—so they can be analyzed on either space.

Another advantage of working with open hypercubes is that they have natural “cubical” compactifications $[0, 1]^S$ that appear to be optimally relevant in the context of mass-action kinetics. Alternatively, we could have achieved a cubical compactification by considering the hypercubes $[0, \infty]^S$. Nevertheless, there is a stylistic advantage to working with the hypercubes $[0, 1]^S$: we can treat symmetrically the cases where a species concentration goes to infinity or to zero. This makes some of our definitions more transparent, and the structural induction becomes cleaner.

Definition 3.1. For any finite nonempty set S , let \mathcal{D}_S be the set of all differential inclusions on the open hypercube $(0, 1)^S$. Fix a collection \mathcal{S} of finite nonempty sets. If \mathcal{X}_S is a set of differential inclusions on $(0, 1)^S$ for each $S \in \mathcal{S}$, then the collection $\mathcal{X} = \{\mathcal{X}_S \subseteq \mathcal{D}_S\}_{S \in \mathcal{S}}$ of sets \mathcal{X}_S is a *family of differential inclusions on open hypercubes indexed by \mathcal{S}* .

3.1 Definitions concerning hypercubes

The definition of vertexical families requires some preliminary notation on hypercubes.

Notation 3.2. Let S be a finite nonempty set.

1. For every $i \in S$, let $e_i \in \mathbb{R}^S$ be the map $S \rightarrow \mathbb{R}$ that sends i to 1 and $S \setminus \{i\}$ to 0.
2. For each subset $U \subseteq S$ and vertex $x \in \{0, 1\}^S$ of the hypercube $[0, 1]^S$, let

$$F_U(x) = (x + \text{span}\{e_i \mid i \in U\}) \cap [0, 1]^S$$

denote the face of the hypercube $[0, 1]^S$ along U at vertex x .

3. For $p = \sum_{i \in S} p_i e_i \in \mathbb{R}^S$, let $|p| = \sqrt{\sum_{i \in S} p_i^2}$ denote its Euclidean norm.
4. For subsets $P, Q \subseteq \mathbb{R}^S$, denote by $d(P, Q) = \inf \{|p - q| \mid p \in P \text{ and } q \in Q\}$ the distance between them.

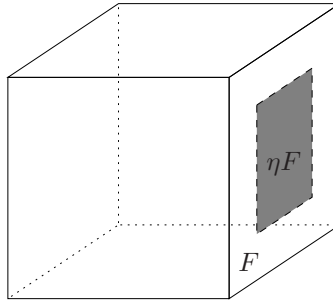
In the context of reaction networks, S indexes the set of reacting chemical species; a chemical complex, being a linear combination of these species, is therefore viewed as a vector in \mathbb{R}^S (see Definition 4.1), which has preferred basis vectors e_i for $i \in S$.

Definition 3.3. Fix a finite nonempty set S . For a face F of $[0, 1]^S$ and a real number $\eta > 1/2$, the *centered shrinking*

$$\eta F = \{x \in F \mid d(x, \partial F) \geq (1 - \eta)/2\}$$

of F is the set of points in F whose distance from the boundary ∂F is at least $(1 - \eta)/2$.

Example 3.4. A centered shrinking of the rightmost face of the 3-cube looks as follows,



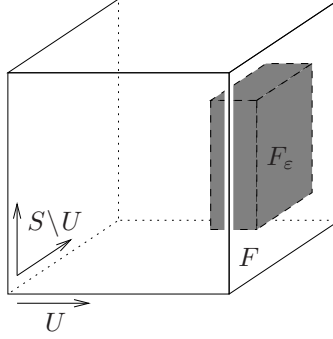
where the inner shaded square is centered in F and has side length η times that of F .

Definition 3.5. Fix a finite nonempty set S and a subset $U \subseteq S$. Let $P \subseteq [0, 1]^S$, and suppose that $\varepsilon \in (0, 1/2) \subset \mathbb{R}$. The ε -pile of the subset P along U is the set

$$\text{pile}(P, \varepsilon, U) := \left\{ x + \sum_{i \in U} \varepsilon_i e_i \mid x \in P \text{ and } -\varepsilon \leq \varepsilon_i \leq \varepsilon \text{ for all } i \in U \right\} \cap [0, 1]^S.$$

Definition 3.6. Fix a finite nonempty set S and a proper face F of the hypercube $[0, 1]^S$ containing a vertex x . Let $U \subseteq S$ be such that $F = F_{S \setminus U}(x)$. For a real number $\varepsilon \in (0, 1/2)$, the ε -block F_ε is pile $((1 - 2\varepsilon)F, \varepsilon, U)$, the ε -pile along U of the centered shrinking $(1 - 2\varepsilon)F$.

Example 3.7. If $\varepsilon = (1 - \eta)/2$ in Example 3.4, the block F_ε looks like the following:



Note that the face F is orthogonal to the basis vector indexed by U , and the thickness ε of the block F_ε equals its distance from the edges of F . The vertex x in Definition 3.6 could equally well be any of the four vertices of F .

Remark 3.8. The block F_ε is a closed subset of $[0, 1]^S$. Such sets are closely related to sets that Pantea [18] denoted by K_ε , which he used for the purpose of projecting trajectories, as we too do in the current paper.

Notation 3.9. Let $f : U \rightarrow S$ be a map of finite sets, and view \mathbb{R}^S as functions $S \rightarrow \mathbb{R}$. Denote by $\pi_f : \mathbb{R}^S \rightarrow \mathbb{R}^U$ the linear projection that sends $v \in \mathbb{R}^S$ to $v \circ f \in \mathbb{R}^U$. When $U \subseteq S$ and f is inclusion, we write π_U for the projection map instead of π_f .

Remark 3.10. If $U \subseteq S$ is any subset, then

1. projection is surjective on the open hypercube: $\pi_U((0, 1)^S) = (0, 1)^U$, and
2. $\pi_U((1 - 2\varepsilon)F_{S \setminus U}(x))$ is a vertex of the hypercube $[0, 1]^U$.

Example 3.11. The projection π_U in Example 3.7 collapses the cube to the horizontal edge



that is $[0, 1] = [0, 1]^U$. The projection takes F as well as the subset $\eta F \subseteq F$ to the indicated right-hand vertex of the interval.

3.2 Definition of vertexical family and main result

The heuristic description of a vertexical family of differential inclusions begins by considering a trajectory of a differential inclusion in the family. Suppose the trajectory remains near a face of the hypercube. The vertexical condition requires that the image of the trajectory under the projection map collapsing that face be the trajectory of a lower-dimensional differential inclusion in the family, up to time reparametrization.

Definition 3.12 (Vertexical family). Let \mathcal{S} be the set of all finite nonempty subsets of the positive integers $\mathbb{Z}_{\geq 1}$. A family $\mathcal{X} = \{\mathcal{X}_S\}_{S \in \mathcal{S}}$ of differential inclusions on open hypercubes indexed by \mathcal{S} is *vertexical* if for each

- set $S \in \mathcal{S}$,
- differential inclusion $X \subseteq T(0, 1)^S$ in \mathcal{X}_S ,
- proper nonempty subset $U \subseteq S$, and
- face $F = F_{S \setminus U}(x)$ of $[0, 1]^S$,

there exists $\varepsilon > 0$ such that for every trajectory $f : I \rightarrow [0, 1]^S$ of X with image in the block F_ε , there exist

- a differential inclusion $Y \in \mathcal{X}_U$,
- a trajectory $g : J \rightarrow [0, 1]^U$ of Y , and
- an order-preserving continuous map $\alpha : I \rightarrow J$

such that $\pi_U \circ f = g \circ \alpha$.

Examples of vertexical families of differential inclusions include those arising from reversible, weakly reversible, endotactic, or strongly endotactic chemical reaction networks (Definitions 4.6 and 5.15); this is the content of Corollary 5.20, the goal of Sections 4 and 5.

Here is our main theorem on abstract vertexical families.

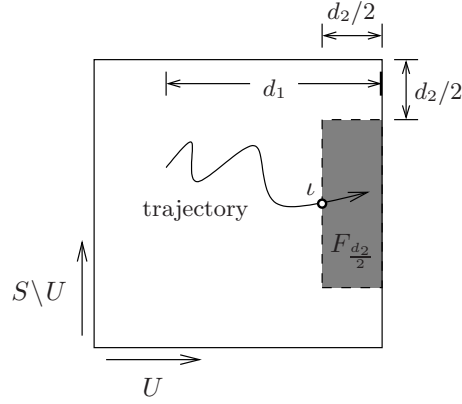
Theorem 3.13. *Fix a vertexical family $\mathcal{X} = \{\mathcal{X}_S\}_{S \in \mathcal{S}}$ on open hypercubes indexed by the set \mathcal{S} of all finite nonempty subsets of the positive integers $\mathbb{Z}_{\geq 1}$. If for every set $S \in \mathcal{S}$, every differential inclusion $X \in \mathcal{X}_S$ is repelled by the vertex set $\{0, 1\}^S$ of its hypercube, then every such X is repelled by, and hence persistent with respect to, the boundary $\partial[0, 1]^S$.*

Proof. Fix $S \in \mathcal{S}$. If S has cardinality 1, then $\partial[0, 1]^S$ repels \mathcal{X}_S by hypothesis. This constitutes the base case for an induction on the cardinality of S that allows us to assume \mathcal{X}_U is repelled by the boundary $\partial[0, 1]^U$ for all proper nonempty sets $U \subset S$, with the goal of proving the result for a given differential inclusion $X \in \mathcal{X}_S$.

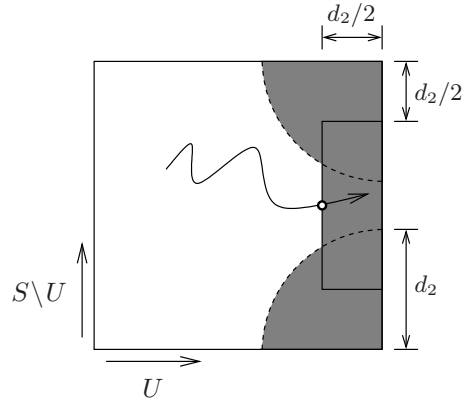
What we actually show is that for every proper, positive-dimensional face $F = F_{S \setminus U}(x)$ of $[0, 1]^S$, if X is repelled by the boundary ∂F of the face then X is repelled by F itself. Given the hypothesis that X is repelled by the vertex set $\{0, 1\}^S$, we deduce by induction on the dimension of F that every proper face of $[0, 1]^S$ is repelling. Since the hypercube $[0, 1]^S$ has only finitely many faces, its entire boundary is therefore repelling, as desired.

Suppose $U \subseteq S$ is a proper nonempty subset, and let $F = F_{S \setminus U}(x)$ be a corresponding face of the hypercube $[0, 1]^S$, parallel to the orthogonal complement of U . Assume that X is repelled by ∂F . Let $f : I \rightarrow (0, 1)^S$ be a trajectory of X , and let $d_1 = d(f(\inf I), F)$ be the distance to F from the initial point of the trajectory. By Remark 2.10, it is enough to exhibit $\varepsilon > 0$, depending only on d_1 , so that the trajectory remains at distance greater than ε from F ; that is, $d(f(I), F) > \varepsilon$.

Since X is repelled by ∂F , Remark 2.10 provides $d_2 > 0$ such that $d(f(I), \partial F) \geq d_2$. Decreasing d_2 if necessary, assume that $d_2 \leq d_1$. Consider the block $F_{d_2/2}$ of F . If the image of the trajectory $f(I)$ does not intersect the block $F_{d_2/2}$, then by defining $\varepsilon = d_2/2$ it follows that $d(f(I), F) > \varepsilon$, and we are done. Therefore, we can and do assume that $I' \subseteq I$ is a nonempty maximal subinterval such that $f(I') \subseteq F_{d_2/2}$, and let $\iota = f(\inf I')$ denote the corresponding initial point, as in the following illustration.



Note that $d(\iota, F) = d_2/2$. Indeed, by maximality of the interval I' the point ι lies on the boundary of $F_{d_2/2}$, and the only boundary face of $F_{d_2/2}$ that intersects the interior $(0, 1)^S$ of the hypercube without also being contained in the d_2 -neighborhood of the boundary ∂F has constant distance $d_2/2$ from F ; see the following illustration.



Because \mathcal{X} is a vertexical family, there exist a differential inclusion Y in \mathcal{X}_U , a trajectory $g : J \rightarrow [0, 1]^U$ of Y , and an order-preserving continuous map $\alpha : I' \rightarrow J$ such that $g \circ \alpha = \pi_U \circ f$ with domain I' . It now suffices to show that there exists $\varepsilon > 0$, depending only on d_2 (which depended only on d_1 ; see Remark 2.10) such that $d(g(J), \pi_U(F)) \geq \varepsilon$, for this claim implies that $d(f(I), F) \geq \varepsilon$, as desired.

To prove the claim, note by hypothesis that Y is repelled by the vertex $\pi_U(F)$ of $[0, 1]^U$. Hence there exists $\varepsilon > 0$ such that all trajectories starting at distance $d_2/2$ away from the vertex $\pi_U(F)$ —and in particular, the trajectory g , because ι has distance precisely $d_2/2$ from F —never get closer than ε to the vertex $\pi_U(F)$. This choice of ε depends only on the distance $d_2/2$, not on any aspect of the particular trajectory f . \square

Remark 3.14. In the statement of Theorem 3.13, if the goal is to prove that a particular differential inclusion $X \in \mathcal{X}_S$ is repelled by (or persistent with respect to) $\partial[0, 1]^S$, then it is enough to assume a slightly weaker hypothesis, namely that (i) X itself is repelled by the vertices $\{0, 1\}^S$ of the hypercube, and (ii) the lower-dimensional set \mathcal{X}_U for each proper nonempty subset $U \subseteq S$ is repelled by the vertices $\{0, 1\}^U$ of its corresponding hypercube.

4 Reaction network theory

In this section, we define reaction networks and their properties. Our networks are more general than usual for chemical reaction network theory [10, 15].

Definition 4.1. Write $\mathfrak{I} = \{(a, b) \mid 0 \leq a < b \leq \infty\}$ for the set of all open subintervals of $\mathbb{R}_{>0}$ and $\mathfrak{I}_{\text{bdd}} = \{[a, b] \mid 0 < a \leq b < \infty\}$ for the set of compact subintervals of $\mathbb{R}_{>0}$.

1. A *reaction network* $(S, \mathcal{C}, \mathcal{R})$ is a triple of finite sets: a set S of *species*, a set $\mathcal{C} \subseteq \mathbb{R}^S$ of *complexes*, and a set $\mathcal{R} \subseteq \mathcal{C} \times \mathcal{C}$ of *reactions*. The *reaction graph* is the directed graph $(\mathcal{C}, \mathcal{R})$ whose vertices are the complexes and whose directed edges are the reactions.
2. A *tempered* reaction network is a reaction network $(S, \mathcal{C}, \mathcal{R})$ together with a *tempering* $\kappa : \mathcal{R} \rightarrow \mathfrak{I}_{\text{bdd}}$ of its reactions by nonempty compact positive intervals.
3. A *meted* reaction network is a reaction network $(S, \mathcal{C}, \mathcal{R})$ together with an *allotment* $\mu : S \rightarrow \mathfrak{I}$ of an open positive interval to each species $s \in S$. The *domain hypercube* of a meted reaction network is the open hypercube $\square^\mu = \prod_{s \in S} \mu(s) \subseteq \mathbb{R}_{>0}^S$.

A reaction $r = (y, y') \in \mathcal{R}$, also written $y \rightarrow y'$, has *reactant* $y = \text{reactant}(r) \in \mathbb{R}^S$, *product* $y' = \text{product}(r) \in \mathbb{R}^S$, and *reaction vector*

$$\text{flux}(r) = \text{product}(r) - \text{reactant}(r).$$

The *reaction diagram* is the realization $(\mathcal{C}, \mathcal{R}) \rightarrow \mathbb{R}^S$ of the reaction graph that takes each reaction $r \in \mathcal{R}$ to $\text{flux}(r)$. A *linkage class* is a connected component of the reaction graph.

Remark 4.2. To explain the motivation for tempered networks, recall that a chemical reaction network gives rise to a dynamical system by way of reaction rates. For biochemical reaction networks, one is typically ignorant of the precise values for the rates. This occurs both because of incomplete information, and because of molecular and environmental variability. One way to model this ignorance is to allow reaction rates $\kappa(r)$ to be time-dependent, as long as they are uniformly bounded away from 0 and ∞ . Craciun, Nazarov, and Pantea called such systems κ -variable [7]. In a similar spirit, we have chosen to work with differential inclusions, allowing $\kappa(r)$ to take on every value from an appropriate interval.

Remark 4.3. Intuitively, one thinks of a meted reaction network as a promise that concentrations of species remain within the allotted intervals. The usual chemical reaction network theory setting would define μ as allotting the entire positive ray $\mathbb{R}_{>0}$ to each species, so that the domain hypercube is the entire positive orthant $\square^\mu = \mathbb{R}_{>0}^S$.

Remark 4.4. The mathematical motivation prompting tempered and meted reaction networks is to ensure that projections of trajectories “stay in the family”. Projections forget the exact concentrations of eliminated species. Absorbing the effect of pre-projection dynamics into post-projection dynamics requires a guarantee that the projected species concentrations never leave a certain sufficiently large interval. Therefore, in post-projection dynamics, the reaction rates remain within appropriately enlarged intervals. Tempered (interval-valued) reaction rates and meted reaction networks provide the extra flexibility for this construction.

This intuition is made precise in Section 5: interval-valued rates allow us to define an appropriate domain category on which mass-action kinetics becomes functorial (Theorem 5.17). As a consequence, projective classes of reaction network (Definition 5.1) give rise to families of differential inclusions that are vertexical.

Remark 4.5. The chemical reaction network theory literature usually imposes the following requirements for a reaction network:

- each complex takes part in some reaction: for all $y \in \mathcal{C}$ there exists $y' \in \mathcal{C}$ such that $(y, y') \in \mathcal{R}$ or $(y', y) \in \mathcal{R}$, and
- no reaction is trivial: $(y, y) \notin \mathcal{R}$ for all $y \in \mathcal{C}$.

Definition 4.1 does *not* impose these conditions; in other words, our reaction graphs may include isolated vertices or self-loops. We drop these conditions to ensure that the projection of a network—obtained by removing certain species—remains a network under our definition even if some reactions become trivial (see Definition 5.1.1). In addition, we allow arbitrary real complexes $y \in \mathbb{R}^S$, so our setting is more general than that of usual chemical reaction networks, whose complexes $y \in \mathbb{Z}_{\geq 0}^S$ are nonnegative integer combinations of species, as in the following definition.

Definition 4.6. A reaction network $(S, \mathcal{C}, \mathcal{R})$ is

1. *integer* if $\mathcal{C} \subseteq \mathbb{Z}^S$.
2. *chemical* if $\mathcal{C} \subseteq \mathbb{Z}_{\geq 0}^S$.
3. *reversible* if the reaction graph of the network is undirected: a reaction (y, y') lies in \mathcal{R} if and only if its reverse reaction (y', y) also lies in \mathcal{R} .
4. *strongly connected* if the reaction graph of the network is strongly connected; that is, if the reaction graph contains a directed path between each pair of complexes.
5. *weakly reversible* if every linkage class of the network is strongly connected.

Note that a network is strongly connected if and only if it is weakly reversible and has only one linkage class.

Definition 4.7. The *stoichiometric subspace* H of a network is the span of its reaction vectors. For a positive vector $x_0 \in \mathbb{R}_{>0}^S$, the *invariant polyhedron* of x_0 is the polyhedron

$$\mathcal{P} = (x_0 + H) \cap \mathbb{R}_{\geq 0}^S .$$

This polyhedron is also referred to as the *stoichiometric compatibility class* in the chemical reaction network theory literature.

Definition 4.8. The standard basis of \mathbb{R}^S indexed by S defines a canonical inner product $\langle \cdot, \cdot \rangle$ on \mathbb{R}^S with respect to which the standard basis is orthonormal. Let $w \in \mathbb{R}^S$.

1. The vector w defines a preorder on \mathbb{R}^S , denoted by \leq_w , in which

$$y \leq_w y' \Leftrightarrow \langle w, y \rangle \leq \langle w, y' \rangle .$$

Write $y <_w y'$ if $\langle w, y \rangle < \langle w, y' \rangle$.

2. For a finite subset $Y \subset \mathbb{R}^S$, denote by $\text{init}_w(Y)$ the set of \leq_w -minimal elements of Y :

$$\text{init}_w(Y) = \{y \in Y \mid \langle w, y \rangle \leq \langle w, y' \rangle \text{ for all } y' \in Y\} .$$

3. For a chemical reaction network $(S, \mathcal{C}, \mathcal{R})$, the set $\mathcal{R}_w \subseteq \mathcal{R}$ of *w-essential reactions* consists of those whose reaction vectors are not orthogonal to w :

$$\mathcal{R}_w = \{r \in \mathcal{R} \mid \langle w, \text{flux}(r) \rangle \neq 0\} .$$

4. The *w-support* $\text{supp}_w(S, \mathcal{C}, \mathcal{R})$ of the network is the set of vectors that are \leq_w -minimal among reactants of w -essential reactions:

$$\text{supp}_w(S, \mathcal{C}, \mathcal{R}) = \text{init}_w(\text{reactant}(\mathcal{R}_w)) .$$

Definition 4.9. Fix a reaction network $(S, \mathcal{C}, \mathcal{R})$.

1. The network $(S, \mathcal{C}, \mathcal{R})$ is *w-endotactic* for some $w \in \mathbb{R}^S$ if

$$\langle w, \text{flux}(r) \rangle > 0$$

for all w -essential reactions $r \in \mathcal{R}_w$ such that $\text{reactant}(r) \in \text{supp}_w(S, \mathcal{C}, \mathcal{R})$.

2. The network $(S, \mathcal{C}, \mathcal{R})$ is *W-endotactic* for a subset $W \subseteq \mathbb{R}^S$ if $(S, \mathcal{C}, \mathcal{R})$ is w -endotactic for all vectors $w \in W$.
3. The network $(S, \mathcal{C}, \mathcal{R})$ is *endotactic* if it is \mathbb{R}^S -endotactic.
4. $(S, \mathcal{C}, \mathcal{R})$ is *strongly endotactic* if it is endotactic and for every vector w that is not orthogonal to the stoichiometric subspace of $(S, \mathcal{C}, \mathcal{R})$, there exists a reaction $y \rightarrow y'$ in \mathcal{R} such that

(i) $y <_w y'$, and

(ii) y is \leq_w -minimal among all reactants in $(S, \mathcal{C}, \mathcal{R})$: $y \in \text{init}_w(\text{reactant}(\mathcal{R}))$.

Remark 4.10. Endotactic chemical reaction networks, which generalize weakly reversible networks, were introduced by Craciun, Nazarov, and Pantea [7, §4]. Our definition is slightly more general still, because we do not require the reaction networks to be chemical (Definition 4.9). Strongly endotactic reaction networks are new; they give rise to strong results concerning permanence using our techniques; see Theorem 6.5.

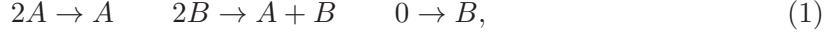
Remark 4.11. For the geometric intuition behind Definition 4.9, imagine a hyperplane normal to w that is sweeping across the reaction diagram in \mathbb{R}^S from infinity in direction w . As this hyperplane sweeps, it stops when it reaches the reactant y of a reaction $y \rightarrow y'$ that is not perpendicular to w . If all such reactions do not point into the halfspace already swept by the hyperplane—that is, all such reactions have product y' outside of the open swept halfspace—then the network is w -endotactic. Equivalently, the network is endotactic if no such reaction makes an obtuse angle with w . Illustrations can be found in [7].

As for strongly endotactic networks, the sweeping hyperplane now stops when it touches the reactant of any reaction, whether or not it is perpendicular to w . Again we require that the products of all such reactions lie outside of the open swept halfspace, and in addition at least one of these reactions is not perpendicular to w . If this condition is satisfied for all vectors w not orthogonal to the stoichiometric subspace, then the network is strongly endotactic.

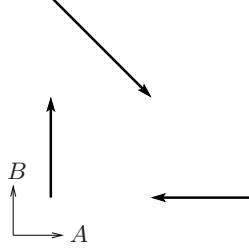
Example 4.12. Here we follow the usual convention of depicting a network by its reaction graph or reaction diagram and writing a complex as, for example, $2A + B$ rather than $y = (2, 1)$. The Lotka–Volterra reaction network, consisting of the three reactions



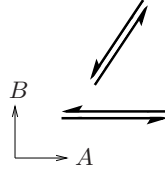
is not endotactic. Reversing all three reactions yields the network



which is strongly endotactic, as can be verified from its reaction diagram:



Example 4.13. Every weakly reversible reaction network is endotactic [7]. However, even a reversible reaction network may fail to be strongly endotactic, as in the following example of a pair of reversible reactions. For $w = (0, 1)$, the \leq_w -minimal reactant complexes are at the bottom, but neither of the corresponding reactions is perpendicular to w .



5 Functoriality of mass-action kinetics

In this section, we assign a differential inclusion to each meted tempered network (Definition 5.15), generalizing the usual mass-action kinetics ODE system in the chemical reaction network theory literature [10, 15]. Viewed appropriately, this assignment of differential inclusions gives mass-action kinetics a functorial nature (Theorem 5.17). Consequently, *projective classes* of reaction networks (Definition 5.1) give rise to vertexical families of differential inclusions (Theorem 5.19). In particular, the reversible, weakly reversible, endotactic, and strongly endotactic chemical reaction networks defined in the previous section all give rise to vertexical families (Corollary 5.20).

5.1 Categorical definitions

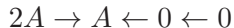
Definition 5.1. Recall, from Definition 3.9, the projection $\pi_U : \mathbb{R}^S \rightarrow \mathbb{R}^U$ for $U \subseteq S$, and denote by $\pi_U^{\times 2} = \pi_U \times \pi_U : \mathbb{R}^S \times \mathbb{R}^S \rightarrow \mathbb{R}^U \times \mathbb{R}^U$ the product of π_U with itself.

1. For a reaction network $(S, \mathcal{C}, \mathcal{R})$, and a nonempty subset $U \subset S$ of species, the *reduced reaction network* is the reaction network $\pi_U(S, \mathcal{C}, \mathcal{R}) = (U, \pi_U(\mathcal{C}), \pi_U^{\times 2}(\mathcal{R}))$.

2. A property P of reaction networks is *projective* if for all finite nonempty sets S , reaction networks $(S, \mathcal{C}, \mathcal{R})$, and nonempty subsets $U \subseteq S$, if $(S, \mathcal{C}, \mathcal{R})$ has property P then the reduced reaction network $\pi_U(S, \mathcal{C}, \mathcal{R})$ has property P .
3. The set of all reaction networks with a given projective property is a *projective class*.

Remark 5.2. The reduced reaction network $\pi_U(S, \mathcal{C}, \mathcal{R})$ is obtained from the reaction network $(S, \mathcal{C}, \mathcal{R})$ by deleting all species outside of U . This concept was defined by Anderson [4, §3.2], who required that any trivial reactions be removed from the reduced reaction set $(\pi_U \times \pi_U)(\mathcal{R})$. In contrast, we allow trivial reactions (Remark 4.5). Another related notion in the context of reversible reactions is that of “reduced event-system” introduced in [1].

Example 5.3. For $U = \{A\}$, the reduced network



of the network (1) in Example 4.12 is obtained by removing species B . The reduced network is strongly endotactic, as is the original network (1).

The implication in Example 5.3 holds in general for strongly endotactic networks.

Lemma 5.4. *The classes of integer, chemical, reversible, strongly connected, weakly reversible, endotactic, or strongly endotactic reaction networks are projective. Further, if P_1 and P_2 are projective properties, then so are the conjunction $P_1 \wedge P_2$ and disjunction $P_1 \vee P_2$.*

Proof. Projectivity holds for integer and chemical networks because projection preserves integrality and nonnegativity of points in \mathbb{R}^S . Projectivity holds for reversible, strongly connected, and weakly reversible networks because these conditions depend only on the reaction graph, on whose vertices and edges projection is surjective.

Next, consider an endotactic network with species set S and the reduced network arising from a nonempty subset $U \subseteq S$. Take any vector $w \in \mathbb{R}^U$. For any reduced reaction $\pi_U(r)$, where r is a reaction in the original network,

$$\langle w, \text{flux}(\pi_U(r)) \rangle = \langle (w, 0), \text{flux}(r) \rangle. \quad (2)$$

Thus, the w -essential reactions of the reduced network are the projections under $\pi_U^{\times 2}$ of the $(w, 0)$ -essential reactions of the original network, where we write $(w, 0) \in \mathbb{R}^U \times \mathbb{R}^{S \setminus U}$. Similarly, the w -support of the reduced network is the projection under π_U of the $(w, 0)$ -support of the original network. So, if $\pi_U(r)$ is a w -essential reaction of the reduced network with reactant in the w -support, then the original reaction r is a $(w, 0)$ -essential reaction of the original network with reactant in the $(w, 0)$ -support. By (2) and the definition of endotactic, $\langle w, \text{flux}(\pi_U(r)) \rangle = \langle (w, 0), \text{flux}(r) \rangle > 0$. Hence the reduced network is endotactic.

Next, let H denote the stoichiometric subspace of a strongly endotactic network, so $\pi_U(H)$ is the stoichiometric subspace of the reduced network. Take a vector $w \in \mathbb{R}^U$ that is

not orthogonal to $\pi_U(H)$. We need only show that there exists a reaction $\pi_U(y) \rightarrow \pi_U(y')$, where $y \rightarrow y'$ is a reaction in the original network, such that $\pi_U(y) <_w \pi_U(y')$ and $\pi_U(y)$ is \leq_w -minimal among all reactant vectors in the reduced network. Again consider $(w, 0) \in \mathbb{R}^U \times \mathbb{R}^{S \setminus U}$. As w is not orthogonal to $\pi_U(H)$, it follows that $(w, 0)$ is not orthogonal to H , and the preorder \leq_w on the reduced reactant complexes is the projection under π_U of the preorder $\leq_{(w,0)}$ on the original reactant complexes. Since the original network is strongly endotactic, there is a reaction $y \rightarrow y'$ in the original network with $y <_{(w,0)} y'$ such that y is $\leq_{(w,0)}$ -minimal among all reactant vectors. This reaction achieves our requirements.

The claim about conjunctions and disjunctions follows formally by Definition 5.1.2. \square

Notation 5.5. Let $I, J \subseteq \mathbb{R}_{\geq 0}$ be two intervals, and S a finite nonempty set.

1. Define $I \cdot J = \{i \cdot j \mid i \in I, j \in J\} \subset \mathbb{R}_{>0}$ and $\bigodot_{s \in S} I_s$ pointwise.
2. For $n \in \mathbb{Z}_{\geq 1}$ define I^n recursively as $I \cdot I^{n-1}$ with $I^1 = I$.
3. $I \times J$ and $\prod_{s \in S} I_s$ denote Cartesian products of intervals, as usual.

Definition 5.6. Let S be a finite nonempty set, and consider a function $\mu : S \rightarrow \mathfrak{I}$ to the set of open positive intervals. A nonempty subset $U \subseteq S$ is μ -projectable if $0 < \inf \mu(s)$ and $\sup \mu(s) < \infty$ for all $s \in S \setminus U$; that is, the left and right endpoints of the intervals $\mu(s)$ are bounded away from 0 and ∞ for those s outside of U .

Remark 5.7. The condition of Definition 5.6 is on the complement $S \setminus U$ because those are the species removed in projecting to U , and so it is those species that must be bounded away from 0 and ∞ . The set S itself is trivially μ -projectable, for all $\mu : S \rightarrow \mathfrak{I}$.

Intuitively, meted tempered networks form a category whose morphisms are projections, where the projection p_U from one object N to another another corresponds to substituting intervals from the allotment of N in place of a set $S \setminus U$ of forgotten species.

Definition 5.8. The category \mathcal{N} of meted tempered reaction networks with projections is given by the following data.

1. Objects: each is an intervalled tempered reaction network N , specified by a reaction network $(S, \mathcal{C}, \mathcal{R})$ along with a tempering $\kappa : \mathcal{R} \rightarrow \mathfrak{I}_{\text{bdd}}$ and an allotment $\mu : S \rightarrow \mathfrak{I}$.
2. Morphisms: $p_U : N \rightarrow N'$ if
 - the network of N' is $(S', \mathcal{C}', \mathcal{R}') = \pi_U(S, \mathcal{C}, \mathcal{R})$ for a μ -projectable subset $U \subseteq S$;
 - the tempering of N' is $\kappa' : \pi_U(r) \mapsto \kappa(r) \cdot \bigodot_{s \in S \setminus U} \mu(s)^{\text{reactant}(r)_s}$, where the exponent on $\mu(s)$ is the component indexed by s in the vector $\text{reactant}(r)$; and
 - the allotment of N' is $\mu' = \mu|_U$, obtained by restricting the allotment of N to U .

Remark 5.9. Composition in \mathcal{N} is well-defined because projecting to $U \subseteq S$ and then projecting to $V \subseteq U$ is the same as projecting directly to V .

In our conception, mass-action kinetics produces from each meted tempered reaction network a differential inclusion on its domain hypercube. Our key observation along these lines, Theorem 5.17, states that mass-action kinetics is a functor, with domain category \mathcal{N} and codomain category as follows.

Definition 5.10. The category \mathcal{DI} of differential inclusions is given by the following data.

1. Objects: each is a choice of manifold with corners and a differential inclusion on it.
2. Morphisms: a morphism from $X \subseteq TM$ to $Y \subseteq TN$ is a continuous map $k : M \rightarrow N$ such that for each trajectory $f : I \rightarrow M$ of X , there is a trajectory $g : J \rightarrow N$ of Y and an order-preserving continuous map $\alpha : I \rightarrow J$ satisfying

$$k \circ f = g \circ \alpha. \quad (3)$$

Lemma 5.11. *Composition of continuous maps induces a well-defined composition on \mathcal{DI} . Specifically, assume $X_j \subseteq TM_j$ for $j = 1, 2, 3$ are differential inclusions, with morphisms $k_{12} : M_1 \rightarrow M_2$ and $k_{23} : M_2 \rightarrow M_3$ in \mathcal{DI} . If $f_1 : I_1 \rightarrow M_1$ is a trajectory of X_1 , then there is a trajectory $f_3 : I_3 \rightarrow M_3$ of X_3 and an order-preserving continuous map $\alpha_{13} : I_1 \rightarrow I_3$ such that the composite continuous map $k_{13} = k_{23} \circ k_{12}$ satisfies $k_{13} \circ f_1 = f_3 \circ \alpha_{13}$.*

Proof. Given f_1 , since k_{12} is a morphism in \mathcal{DI} , there is a trajectory $f_2 : I_2 \rightarrow M_2$ of X_2 and a continuous order-preserving map $\alpha_{12} : I_1 \rightarrow I_2$ such that $k_{12} \circ f_1 = f_2 \circ \alpha_{12}$. For the desired trajectory $f_3 : I_3 \rightarrow M_3$ of X_3 use the one afforded by virtue of k_{23} being a morphism in \mathcal{DI} , given f_2 , which comes with a continuous order-preserving map $\alpha_{23} : I_2 \rightarrow I_3$ such that $k_{23} \circ f_2 = f_3 \circ \alpha_{23}$. Set $\alpha_{13} = \alpha_{23} \circ \alpha_{12}$. Then

$$\begin{aligned} k_{13} \circ f_1 &= k_{23} \circ k_{12} \circ f_1 \\ &= k_{23} \circ f_2 \circ \alpha_{12} \\ &= f_3 \circ \alpha_{23} \circ \alpha_{12} \\ &= f_3 \circ \alpha_{13}, \end{aligned}$$

as desired. □

Remark 5.12. Compare the notion of morphism in \mathcal{DI} (Definition 5.10) with that of vertexical family (Definition 3.12). Equation (3) also occurs in Definition 3.12, with k being a particular type of continuous map π_U . However, Definition 5.10 asks for a global map k , whereas the maps in Definition 3.12 are required only locally, on blocks of faces.

Remark 5.13. One motivation for defining the category of differential inclusions this way comes from the dynamical systems concept of *topological equivalence* [16], which identifies two phase portraits as qualitatively the same, even if the details of the dynamics may differ. The isomorphisms in our category \mathcal{DI} correspond exactly to topological equivalence.

For this reason, morphisms between differential inclusions may also be called *topological morphisms*. Intuitively, if a topological morphism is a monomorphism, then its target differential inclusion qualitatively simulates the domain differential inclusion. Maps that are not monomorphisms can of course result in the loss of information, in general. The categorical message of Theorem 3.13 is that it is sometimes possible to piece together many “lossy” maps on the same domain to regain substantial information about the domain dynamics.

Another concept from dynamical systems, *topological congruence* [16], is a stronger notion than topological equivalence that disallows time reparameterization. This motivates looking at a subcategory \mathcal{DI}_1 of \mathcal{DI} in which the order-preserving map α in Definition 5.10 is required to be the identity map; the definition follows.

Definition 5.14. The *category \mathcal{DI}_1 of differential inclusions with topological congruence morphisms* is the subcategory of \mathcal{DI} with the following data.

1. Objects: the same objects as in \mathcal{DI} .
2. Morphisms: a morphism from $X \subseteq TM$ to $Y \subseteq TN$ is a continuous map $k : M \rightarrow N$ such that $k \circ f$ is a trajectory of Y whenever $f : I \rightarrow M$ is a trajectory of X .

The proof of Lemma 5.11 makes it plain that any composition in \mathcal{DI} of morphisms in \mathcal{DI}_1 is a morphism in \mathcal{DI}_1 , because every reparameterization map α_{ij} in that proof can be taken to be the identity map on I_1 .

Definition 5.15. The *mass-action differential inclusion* of a meted tempered reaction network N , specified by a reaction network $(S, \mathcal{C}, \mathcal{R})$ with tempering κ and allotment μ , is the differential inclusion on the domain hypercube $\square^\mu \subseteq \mathbb{R}_{>0}^S$ whose fiber over $x \in \square^\mu$ is

$$\left\{ \sum_{r \in \mathcal{R}} k_r \text{flux}(r) x^{\text{reactant}(r)} \mid k_r \in \kappa(r) \text{ for all } r \in \mathcal{R} \right\} \subseteq \mathbb{R}^S = T_x \square^\mu.$$

The *mass-action functor* $\mathfrak{M} : \mathcal{N} \rightarrow \mathcal{DI}_1$ is defined on

1. objects N by setting $\mathfrak{M}(N)$ equal to the mass-action differential inclusion of N , and on
2. morphisms $p_U : N \rightarrow N'$ by setting $\mathfrak{M}(p_U)$ equal to the projection $\pi_U : \square^\mu \rightarrow \square^{\mu'}$.

Remark 5.16. The usual mass-action kinetics ODEs are the special cases where the tempering κ assigns not an interval of positive length but a point—the reaction rate constant—to each reaction, and the domain hypercube is the entire positive orthant: $\square^\mu = \mathbb{R}_{>0}^S$.

5.2 Functorial results and consequences

Theorem 5.17. *The mass-action functor \mathfrak{M} is a functor from the category \mathcal{N} of meted tempered reaction networks with projection morphisms to the category \mathcal{DI}_1 of differential inclusions with topological congruence morphisms.*

Proof. The content of the statement is twofold: first, that $\mathfrak{M}(p_U) = \pi_U$ in Definition 5.15.2 indeed defines a morphism $\mathfrak{M}(N) \rightarrow \mathfrak{M}(N')$, and second, that \mathfrak{M} preserves identity morphisms as well as compositions. The second is straightforward (projections are sent to projections). For the first, it suffices to observe that for any nonempty $U \subseteq S$, the projection $\pi_U \circ f$ of a trajectory f of $\mathfrak{M}(N)$ is a trajectory of $\mathfrak{M}(p_U(N))$ by definition of p_U . \square

Vertexical families are defined in terms of differential inclusions on unit hypercubes $(0,1)^S$. In contrast, the mass-action functor produces differential inclusions on positive orthants $\mathbb{R}_{>0}^S$. To translate back and forth, our next definition fixes a smooth, order-preserving diffeomorphism $\ell : \mathbb{R}_{>0} \rightarrow (0,1)$. The actual choice is irrelevant for our purposes, but if it helps, the reader may consider the function $x \mapsto x/(1+x)$.

Definition 5.18. Fix a smooth, order-preserving diffeomorphism $\ell : \mathbb{R}_{>0} \rightarrow (0,1)$. For every nonempty finite set S , let $\ell^S : \mathbb{R}_{>0}^S \rightarrow (0,1)^S$, with derivative $d\ell^S : T\mathbb{R}_{>0}^S \rightarrow T(0,1)^S$.

1. The *pushforward* of a differential inclusion X on $\mathbb{R}_{>0}^S$ under ℓ is the differential inclusion $d\ell^S(X)$ on $(0,1)^S$.
2. For a meted tempered reaction network N defined on a species set S with allotment μ , the differential inclusion $\mathfrak{M}^\ell(N)$ is the pushforward of the mass-action differential inclusion $\mathfrak{M}(N)$, considered as a differential inclusion on the image $\ell^S(\square^\mu) \subseteq (0,1)^S$ of the domain hypercube \square^μ under ℓ .

The following is the main result of this section.

Theorem 5.19. *Let P be a projective property of reaction networks. If \mathcal{F}_P is the class of all meted tempered reaction networks whose underlying reaction networks have property P and whose domain hypercubes equal the entire (open) positive orthant, then $\mathfrak{M}^\ell(\mathcal{F}_P) = \{\mathfrak{M}(N) \mid N \in \mathcal{F}_P\}$ is a vertexical family of differential inclusions on open hypercubes.*

Proof. By definition, $\mathfrak{M}^\ell(\mathcal{F}_P)$ is a family of differential inclusions on open hypercubes. Hence we need only prove $\mathfrak{M}^\ell(\mathcal{F}_P)$ is vertexical. Consider a meted tempered reaction network $N \in \mathcal{F}_P$, specified by a reaction network $(S, \mathcal{C}, \mathcal{R})$ with tempering κ and allotment μ . Fix a proper nonempty subset $U \subset S$ and a vertex $x \in \{0,1\}^S$ of the hypercube $(0,1)^S$. Denote by $F = F_{S \setminus U}(x)$ the corresponding face of the hypercube.

Fix $0 < \varepsilon < \frac{1}{2}$, and define $\mu' = \mu'_{\varepsilon, U} : S \rightarrow \mathfrak{I}$ by

$$\mu'(s) = \begin{cases} \mu(s) & \text{if } s \in U \\ \ell^{-1}(\varepsilon, 1 - \varepsilon) & \text{if } s \in S \setminus U \end{cases}$$

recalling that $\mu(s) = (0, \infty)$ for all $s \in S$. Denote by N' the meted tempered reaction network N' that agrees with N except that the allotment of N' is μ' instead of μ . The underlying reaction network of N' still has property P , because N and N' have the same underlying reaction network.

While N' itself no longer has the entire positive orthant $\mathbb{R}_{>0}^S$ as its domain hypercube, the set U is μ' -projectable (Definition 5.6), and the reduced network $p_U(N')$ has domain hypercube $\mathbb{R}_{>0}^U$. Since P is projective, $p_U(N')$ therefore lies in \mathcal{F}_P . Consequently, by definition of vertexical family (Definition 3.12), it is enough to show that for any trajectory $f : I \rightarrow F_\varepsilon$ of $\mathfrak{M}^\ell(N)$ with image in the block F_ε , the projection $p_U \circ f = g$ is a trajectory of the mass-action differential inclusion $\mathfrak{M}^\ell(p_U(N'))$.

The trajectory f is also a trajectory of $\mathfrak{M}^\ell(N')$, since $F_\varepsilon \subseteq \ell^S(\square^{\mu'})$ by construction of μ' . The result is now deduced easily from functoriality of mass-action kinetics (Theorem 5.17): the morphism π_U in the category \mathcal{DI}_1 from $\mathfrak{M}(N')$ to $\mathfrak{M}(p_U(N'))$ yields the pushforward morphism $\mathfrak{M}^\ell(N') \rightarrow \mathfrak{M}^\ell(p_U(N'))$ in \mathcal{DI}_1 , so the proof is complete by definition of morphisms in the category \mathcal{DI}_1 (Definition 5.14.2). \square

Recall that in propositional logic, a monotone (or monotonic) formula is one formed by the application of AND and OR operations only, without the use of NOT operations.

Corollary 5.20. *The classes of (monotone combinations of) integer, chemical, reversible, strongly connected, weakly reversible, endotactic, or strongly endotactic tempered reaction networks on positive orthants generate vertexical families of differential inclusions.*

Proof. Immediate from Theorem 5.19 and Lemma 5.4. \square

Remark 5.21. The category \mathcal{N} of networks with projections suffices for our purposes, but it would be more natural to allow tempered reaction networks with an associated domain set $D \subseteq \mathbb{R}_{>0}^S$ that is not necessarily a Cartesian product of intervals. In addition, it is tempting to add to the category more morphisms, such as those corresponding to translation of the reaction diagram within \mathbb{R}^S , or scaling, rotation, arbitrary linear maps, graph homomorphisms, inversion $z = 1/x$, and so on. It is easy to verify that translation acts as a time-reparametrization. Hence, even allowing translations, mass-action kinetics remains a functor to \mathcal{DI} . This leads to the following problem, which we leave open.

Question 5.22. *What is the richest domain category for which mass-action kinetics remains a functor to the category \mathcal{DI} of differential inclusions?*

This question is important because a richer domain category would imply more ways of reducing the behavior of a network's mass-action kinetics to the behaviors of related networks. This could allow us to “program” (and analyze) instances of reaction dynamics in high dimensions as appropriate combinations of simpler reaction dynamics.

Remark 5.23. Consider a vertexical family of mass-action differential inclusions for which the one-dimensional differential inclusions in the family are known to be permanent. For instance, the differential inclusions arising from weakly reversible, endotactic, or strongly endotactic networks have this attribute. It is tempting to attempt to argue that such a family is permanent by the following induction: given a trajectory, all of its one-dimensional projections (which are also in the family, due to the functoriality of mass-action kinetics and projectivity of the relevant properties) are permanent, and hence the trajectory itself must be permanent. However, this does not work because of uniformity issues. It is true that for a given trajectory, there exists a compact set that it enters eventually. However, what we need is one compact set so that every trajectory eventually enters this set, and our inductive argument does not prove this. A successful argument about permanence requires additional structure; for example, see Remark 6.4.

6 Implications for persistence of mass-action systems

One of the long-standing open problems of chemical reaction network theory is the global attractor conjecture concerning so-called “complex-balanced systems”. Complex-balanced systems form a well-studied subclass of weakly reversible mass-action ODE systems that contain all so-called “detailed-balanced” systems and weakly reversible “deficiency zero” systems. Many properties about complex-balanced systems (as well as detailed-balanced systems and deficiency zero systems) were elucidated by Feinberg, Horn, and Jackson in the 1970s, and we provide only an overview here. (See any of the references [8, 9, 10, 15] for a definition of complex-balanced systems.)

For complex-balanced systems, it is known that there is a unique steady state within the interior of each invariant polyhedron \mathcal{P} . This steady state is called the Birch point in [8] due to the connection to Birch’s Theorem in algebraic statistics. Moreover, a strict Lyapunov function exists for this point, so local asymptotic stability relative to \mathcal{P} is guaranteed [10, 15] (see Remark 6.4). An open question is whether all trajectories with an initial condition in the interior of \mathcal{P} converge to the unique Birch point of \mathcal{P} . The assertion that the answer is “yes” is the content of the following conjecture, which was stated first by Horn in 1974 [14] and given the name “Global Attractor Conjecture” by Craciun, et al. [8].

Conjecture 6.1 (Global Attractor Conjecture). *For any complex-balanced mass-action system $(S, \mathcal{C}, \mathcal{R}, \kappa)$ and any strictly positive initial condition x^0 , the Birch point $\bar{x} \in \mathcal{P} := (x^0 + H) \cap \mathbb{R}_{\geq 0}^S$ is a global attractor of the relative interior of the invariant polyhedron $\text{int}(\mathcal{P})$.*

In 1989, Feinberg [11] conjectured that all mass-action ODE systems arising from weakly reversible reaction networks are persistent, and observed that the persistence of weakly reversible reaction networks would imply the global attractor conjecture. This reduced the problem of proving the global attractor conjecture to the problem of establishing persistence for weakly reversible mass-action systems. Our functoriality results reduce persistence to

bounding the dynamics away from vertices of the hypercube—so it suffices to ensure that all species remain bounded away from 0 and ∞ in the positive orthant—at the price of considering tempered reaction networks.

Corollary 6.2. *Let \mathcal{F} be the class of all tempered reaction networks that are one or more of the following: integer, chemical, reversible, strongly connected, weakly reversible, endotactic, or strongly endotactic. If the mass-action differential inclusions on positive orthants of all reaction networks in \mathcal{F} are repelled by vertices after pushing forward to open hypercubes by a smooth order-preserving diffeomorphism, then they are repelled by the entire boundary.*

Proof. Immediate from Theorem 3.13 and Corollary 5.20. \square

Recently, Craciun, Nazarov, and Pantea [7] generalized Feinberg’s persistence conjecture in the following three ways: the weakly reversible hypothesis is weakened to endotactic, fixed reaction rate constants are allowed to vary within bounded intervals (i.e., the network is tempered), and the conclusion of persistence is strengthened to permanence [7, §4]. We present an extended version of their conjecture that drops the requirement that the reaction network be chemical.

Conjecture 6.3 (Extended Permanence Conjecture). *If \mathcal{F} is the family of meted tempered endotactic reaction networks whose domain hypercube is the entire positive orthant $\mathbb{R}_{>0}^S$, then $\mathfrak{M}^\ell(\mathcal{F})$ is permanent.*

Remark 6.4. Horn and Jackson [15] established that any complex-balanced mass-action ODE system N on a species set S admits the strict Lyapunov function

$$g_\alpha(x) = \sum_{i \in S} x_i \left(\log \frac{x_i}{\alpha_i} - 1 \right) ,$$

where $\alpha \in \mathbb{R}_{>0}^S$ is a given complex-balanced steady state of N . Consequently, the differential inclusion $\mathfrak{M}^\ell(N)$ is vertex-repelling (see Definition 5.18). The proof, which is due in part to Anderson and Craciun et al. [3, 8], proceeds by showing that the Lyapunov function g_α has a local maximum at the vertex 0 as well as bounded level sets that do not allow trajectories to escape to infinity.

If the class of complex-balanced systems were projective, then our arguments would have proved the global attractor conjecture. However, this is not the case: projections of complex-balanced systems need not be complex-balanced. Endotactic networks, however, do constitute a projective class, and, in our view, it is this property that allowed Craciun, Nazarov, and Pantea to make their projection-type arguments [7, 18]. Similarly, the property of having only one linkage class is projective: a network with only one linkage class maintains this property after reduction. This was used in Anderson’s proof of the global attractor conjecture for networks possessing only one linkage class [4].

Conjectures 6.1 and 6.3 both remain open; for an overview of recent progress on these problems, we refer the reader to the work of Anderson [3, §1.1]. However, using the results presented in the current paper, we prove the following in a subsequent paper [13].

Theorem 6.5. *If \mathcal{F} is the family of meted tempered strongly endotactic reaction networks whose domain hypercube is the entire positive orthant $\mathbb{R}_{>0}^S$, then $\mathfrak{M}^\ell(\mathcal{F})$ is permanent.*

The key step contributed by the results in the current paper is Corollary 6.2 in the case of strongly endotactic networks. The approach in [13] shows that for the mass-action differential inclusions of strongly endotactic networks, outside a compact set the function $g_\alpha(x)$ in Remark 6.4 continues to behave like a Lyapunov function. Theorem 6.5 is established by an argument along the lines suggested in Remark 6.4.

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